European Heart Journal (2010) **31**, 530–541
doi:10.1093/eurheartj/ehp605

REVIEW

Controversies in Cardiovascular Medicine

Chronic stable coronary artery disease: drugs vs. revascularization

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Received 10 September 2009; revised 22 November 2009; accepted 11 December 2009; online publish-ahead-of-print 26 January 2010

Coronary artery disease remains the leading cause of mortality in most industrialized countries, although age-standardized mortality related to coronary artery disease (CAD) has decreased by more than 40% during the last two decades. Coronary atherosclerosis may cause angina pectoris, myocardial infarction, heart failure, arrhythmia, and sudden death. Medical management of atherosclerosis and its manifestation aims at retardation of progression of plaque formation, prevention of plaque rupture, and subsequent events and treatment of symptoms, when these occur as well as treatment of the sequelae of the disease. Revascularization by either percutaneous coronary intervention (PCI) or coronary artery bypass surgery (CABG) is performed as treatment of flow-limiting coronary stenosis to reduce myocardial ischaemia. In high-risk patients with acute coronary syndromes (ACS), a routine invasive strategy with revascularization in most patients provides the best outcome with a significant reduction in death and myocardial infarction compared with an initial conservative strategy. Conversely, the benefit of revascularization among patients with chronic stable CAD has been called into question. This review will provide information that revascularization exerts favourable effects on symptoms, quality of life, exercise capacity, and survival, particularly in those with extensive CAD and documented moderate-to-severe ischaemia. Accordingly, CABG and PCI should be considered a valuable adjunct rather than an alternative to medical therapy.

Keywords Coronary artery disease • Revascularization • Percutaneous coronary interventions • Stents • Drug-eluting stents • Coronary artery bypass grafting

Introduction

Coronary artery disease (CAD) remains the leading cause of mortality in most industrialized countries, although age-standardized mortality related to CAD has decreased by more than 40% during the last two decades.[1,2] Half of this decline resulted from prevention and reduction in major risk factors, whereas the other half has been attributed to medical treatment and revascularization.[3] Coronary artery disease is the result of atherosclerosis, a progressive disorder of the vessel walls, with formation of plaques throughout the arterial system.[4] Vascular inflammation may lead to disruption of the endothelium overlying a plaque and cause subsequent intravascular thrombosis.[5,6] Symptoms related to atherosclerosis vary depending on the location and degree of stenosis of the vessels and the occurrence, site, and severity of plaque disruption. Coronary atherosclerosis may thus be asymptomatic or cause angina pectoris, myocardial infarction (MI), heart failure, arrhythmias, and sudden death.[4] *Medical management* of atherosclerosis and its manifestation aims at retardation of progression of plaque formation, prevention of plaque rupture, and subsequent events and treatment of symptoms, when these occur as well as treatment of the sequelae of the disease. *Revascularization* by either percutaneous coronary intervention (PCI) or coronary artery bypass surgery (CABG) is performed as treatment of flow-limiting coronary stenosis to reduce myocardial ischaemia and its manifestations.

In high-risk patients with acute coronary syndromes (ACS, with or without ST-segment elevation) a routine invasive strategy with revascularization in most patients provides the best outcome with a significant reduction in death and MI compared with an initial conservative strategy.[7–10] Conversely, the benefit of revascularization among patients with chronic stable CAD has been called into question (*Table 1*).[11–13] In particular, the appropriateness of PCI has been challenged because many patients undergoing PCI lack documentation of ischaemia by non-invasive testing prior to the procedure,[14] the incremental cost,[15] and an alleged lack of survival benefit.[12,16,17] Therefore, in this review we discuss the indications for

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Table 1 Clinical presentation and indication for percutaneous coronary interventions in recent all-comer trials and registries in Europe

	EuroHeart Survey[120]	SIRTAX[121]	BASKET[122]	LEADERS[123]
Chronic stable CAD, %	53	49	42	45
Unstable angina/non-ST elevation MI, %	30	29	36	39
ST-elevation MI, %	16	22	21	16

Approximately half of procedures are performed in patients with acute coronary syndromes, whereas the other half of interventions are in the setting of chronic stable coronary artery disease.
CAD, coronary artery disease; MI, myocardial infarction.

revascularization in patients with 'stable' CAD, in the context of the incidence of angina pectoris and its prognosis, as well as established and new anti-angina drugs. Preventive medical therapy is well described in current guidelines and outside the scope of this review.[18]

Prevalence, incidence, and prognosis of angina pectoris

The prevalence of CAD varies widely across Europe, with high rates in the northern and eastern countries and lower rates in the south and west.[19] Overall the prevalence of angina is estimated at 20–40 per 1000 inhabitants. It is higher in men than in women at a similar age, and varies 10-fold between the ages of 50 and 70 years.[20] A recent study from Finland describes the incidence of angina as a first manifestation of CAD.[21] The incidence calculated from new prescriptions of nitrates was remarkably similar among men and women. In contrast, the incidence of new angina defined by an abnormal stress test was almost twice as high in men, as in women. This confirms earlier reports of underuse of diagnostic tests in women.[20] Overall the incidence of angina by either definition varied from 4–7 at age 45–54 to 42–45 at age 85–89. The age of new angina was lower in men (68 $\pm$ 11 years) than in women (72 $\pm$ 10 years). However, the prognostic implications were similar in both sexes.[21] Patients with angina had a substantially higher mortality risk than the average population, with standard mortality rates around 2–5 at age 45–65, and around 1–2 at age 75–89.

While mortality rates for acute manifestations of CAD have declined in recent years, mortality from stable CAD has not changed significantly over the last decades.[22] Furthermore it should be noted that in the Finnish study, the rate of fatal and non-fatal MI was higher than the rates reported in recent clinical trials of patients with angina or stable CAD.[21,23–25] This underscores the fact that trials include selected groups of patients, often at lower risk than those in actual clinical practice.

Pathophysiology of stable coronary artery disease

Assessment of the severity of coronary artery disease

Advanced age, left-ventricular function (ejection fraction), and the extent and severity of coronary stenosis as assessed at the time of diagnostic coronary angiography and the presence or absence of more extensive atherosclerosis in other vascular beds are the most important prognostic factors in patients with established CAD.

Several risk-scores, based on clinical factors have been proposed to predict the risk for MI or death in patients with stable CAD.[26] Also a simple classification into single-, double-, triple-, and left main CAD is clinically useful and is a major prognostic indicator during long-term follow-up of angiography studies.[27,28] Additional prognostic information is provided by the severity of coronary artery obstruction and its location, which are combined in the CAD jeopardy score, the Duke prognostic CAD index, and more recently the SYNTAX score.[29–32] Taken together these data provide a gradient of risk with more extensive and severe CAD portending worse prognosis.

Assessment of lesion severity is mostly based on coronary angiography, while the structure of the vessel wall and plaque morphology may be studied with intravascular ultrasound or optical coherence tomography.[33,34] Obstructive coronary artery lesions progressively restrict the ability to increase blood flow in response to changing metabolic demands and lead to myocardial ischaemia at rest or during exercise.[35] Generally, compensatory vasodilatory mechanisms are exhausted with lesions exceeding 80% of lumen diameter,[36] while dysfunction of the endothelium or spasm may aggravate a stenosis caused by a coronary plaque (*Figure 1*).[37,38]

The advent of sensor-tipped guidewires allows for physiological determination of lesion significance by measuring fractional flow reserve (FFR) during pharmacologically induced maximal hyperaemia.[39] A threshold of FFR $<$80% has been correlated with ischaemia as detected by nuclear imaging procedures or stress echocardiography and constitutes a criterion for revascularization.[40]

Manifestations of chronic myocardial ischaemia

Myocardial ischaemia typically elicits a cascade of events characterized by diastolic and systolic ventricular dysfunction with regional wall motion abnormalities, ST-segment changes, and the development of ischaemic pain (angina pectoris). Prolonged myocardial ischaemia causes myocardial cell death.[41]

Chronic CAD is by far the commonest cause of heart failure.[42] Even in patients with a diagnosis of idiopathic dilated

cardiomyopathy CAD is frequently found at autopsy.[43] Chronic or repetitive reduction of myocardial perfusion owing to severely obstructed coronary arteries or collateralized total occlusions may result in non-contractile but viable myocardium, which recovers after coronary revascularization, a process referred to as 'hibernation'.[44,45] In two-thirds of patients with stable CAD and left-ventricular dysfunction a decline in left-ventricular ejection fraction was observed during the waiting period prior to CABG, which resolved at least in part following revascularization.[46]

Plaque rupture and erosion with thrombotic complications are a frequent cause of MI and sudden death.[6,47] However, ruptured plaques may go clinically undetected and heal (*Figure 2*).[48] This was confirmed in recent clinical studies using *in vivo* imaging which identified superimposed layers of necrotic areas covered by fibrosis.[49] Post-mortem examination of patients who died of acute MI showed severe underlying coronary artery narrowing with a mean diameter stenosis of 91% (range 67–99%) at sites of plaque rupture.[50] In contrast, MI in patients most often occurs by plaque rupture and thrombosis at a 'non significant' lesion, i.e. a plaque with <50% coronary stenosis at angiography.[5,6,47] While non-obstructive atherosclerotic lesions are by far more prevalent in the general population than severe lesions and therefore frequently encountered in ACS patients, high-grade coronary artery stenoses are hazardous and play an ominous role in sudden death and fatal MI.[48,51] These observations support the concept of revascularization by PCI or CABG of coronary lesions causing myocardial ischaemia whether or not angina is present, provided that such ischaemia is documented in that patient.

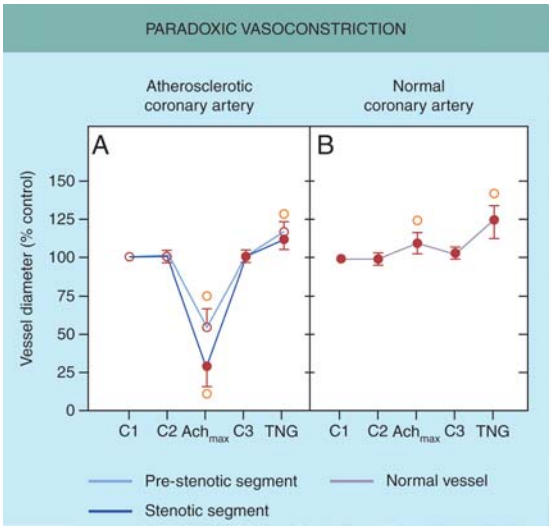

Figure 1 Endothelial dysfunction in vessels with atherosclerotic coronary artery disease. Intracoronary infusion of acetylcholine elicits vasodilatation in normal coronary arteries, but paradoxical vasoconstriction in vessels with coronary atherosclerosis due to insufficient nitric-oxide supply. Obtained with permission from Ludmer *et al.*[38]

Medical treatment of coronary artery disease and angina pectoris

In addition to a healthy lifestyle, drug therapy aims at retardation of progression of atherosclerosis, or perhaps even its regression, and at prevention of cardiovascular events such as death, MI, or stroke.[18,52] Preventive treatment includes aspirin, statins, ACE-inhibitors, angiotensin receptor blockers, and β blockers in patients after MI[53] and patients with heart failure. In addition, clopidogrel, prasugrel, and ticagrelor reduce recurrent events in the first year after an ACS.[54–56] It should be appreciated that these drugs, apart from β blockers, do not reduce angina pectoris or ischaemia when present.

The numbers needed to treat with these drugs depend on the risk for future events of a specific patient group. Patients with stable CAD included in the recent ACTION or EUROPA trials, who already received different preventive drugs, had an annual risk of cardiovascular death or MI of about 2.5%.[24–26] To avoid one such event, about 175 patients should be treated during 1 year with aspirin (relative risk reduction 23%), about 120 patients with a 'standard dose' statin (RRR 30%), 200 with an ACE inhibitor

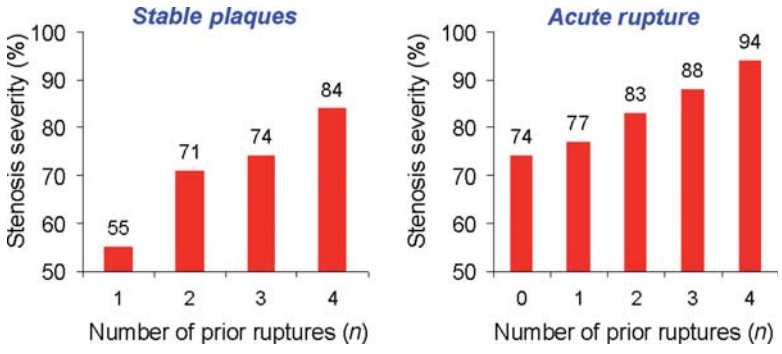

Figure 2 Relationship of stenosis severity and number of preceding plaque ruptures. Data derived from an autopsy study of patients dying from sudden cardiac death. (Burke *et al.*[48]) Stenosis severity positively correlates with the number of previous plaque ruptures for both stable plaques and those with acute plaque rupture.

or AT2 receptor blocker (RRR 20%), 200 patients with clopidogrel in the first year after ACS (RRR 20%), and 240 with high dose statin (RRR 15% when compared with lower statin dose). In patients at higher risk, the numbers needed to treat are obviously lower, and treatment is more cost-effective.

Immediate relief of angina can be provided by nitroglycerine, isosorbide mononitrate, or chewing a nifedipine capsule. Patients may also be instructed to use these short acting drugs prior to exercise, in order to reduce the likelihood of subsequent angina. In symptomatic patients the frequency of episodes of angina and nitroglycerine consumption can be reduced by long acting nitrates, β blockers, and calcium antagonists.[52] These well-established agents improve exercise tolerance during a stress test, and reduce the need for revascularization by PCI or CABG.[23]

Recently two new classes of drugs have been introduced which have similar effects as the established agents, albeit through completely different modes of action.

These drugs have not yet been evaluated by the ESC guideline committee. Ivabradine reduces heart rate (sinus rhythm) at rest as well as during exercise by inhibition of the If current in the sino-atrial node, without any effect on blood pressure, intracardiac conduction, QT interval, or myocardial contractility. In a series of clinical trials ivabradine reduced nitroglycerine consumption and improved exercise tolerance during a stress test when compared with placebo in patients with different background therapies.[57–59] In comparative studies ivabradine was equally effective as atenolol or amlodipine mono-therapy.[58] In a large clinical trial in patients with left-ventricular dysfunction, ivabradine was safe, even when given in combination with β blockers and reduced the number of revascularization procedures during follow-up, in particular in patients with a resting heart rate above 70 b.p.m., but it did not reduce the rates of cardiovascular death of MI.[60] Up to 25% of patients receiving ivabradine experience flashes in the eye or other mild visual symptoms which disappear at continuation of therapy and rarely are a reason to discontinue the drug.[60]

Ranolazine selectively inhibits the late sodium influx in the myocardium, which is increased during myocardial ischaemia.[61] Thus ranolazine attenuates the ischaemic abnormalities of ventricular repolarization and the resulting reduced contractility. In clinical trials ranolazine improves exercise tolerance and reduces the frequency of angina episodes compared with placebo in patients with angina pectoris.[61] Side effects include nausea, dizziness, and asthenia. Ranolazine causes some prolongation of the QT interval; however, no significant arrhythmias have been reported. In a large clinical trial in patients after an ACS no significant reduction in subsequent death or MI was observed.[62]

Revascularization in stable coronary artery disease

Revascularization, relief of ischaemia, and prognosis

The principal goal of revascularization is the relief of ischaemia to improve quality of life and exercise capacity, to reduce the amount of anti-angina drugs, and ultimately improve prognosis on top of the beneficial effects of medical treatment. Symptomatic and asymptomatic ischaemia are of prognostic importance in patients with CAD particularly when occurring at low workload.[63,64] Revascularization, by eliminating the target lesion (PCI) or bypassing the narrowed epicardial vessel (CABG), more effectively relieves myocardial ischaemia than medical treatment alone (*Table 2*). For example, in the randomized Asymptomatic Cardiac Ischemia Pilot (ACIP) study, 57% of patients treated with revascularization were free of ischaemia at 1 year compared with 31 and 36% in the ischaemia-guided and angina-guided strategies, respectively ($P < 0.0001$). Furthermore, at 2 years follow-up, the risk of death and MI was significantly lower among patients undergoing revascularization (4.7%) compared with those receiving ischaemia-guided (8.8%) or angina-guided medical treatment (12.1%, $P < 0.04$).[65] Similarly, patients with silent ischaemia after recent MI enrolled into the randomized SWISSI II trial showed lower rates of ischaemia when allocated to PCI (12%) than medical treatment (29%, $P = 0.03$), a beneficial effect accompanied by improved left-ventricular ejection fraction (57 vs. 49%, $P < 0.001$) and an absolute reduction in clinical events (cardiac death, MI, and revascularization) of 6.3% per year in favour of PCI.[66] Along the same line, patients with angina or exercise-induced ischaemia early after MI had a better prognosis after revascularization than with medical therapy alone in the DANAMI study.[67] In the myocardial perfusion substudy of COURAGE, PCI compared with medical treatment showed a greater absolute reduction in myocardial ischaemia (-2.7 vs. -0.5%, $P < 0.0001$), and more patients exhibited a relevant reduction in ischaemia (33 vs. 19%, $P = 0.0004$), particularly among those with moderate to severe ischaemia (78 vs. 52%, $P = 0.007$).[68] Again, there was a graded relationship between reduction of ischaemia and subsequent risk of death or MI with improved event-free survival in patients with significant reduction of ischaemia.[68]

Various observational studies have addressed the impact of revascularization on prognosis. A myocardial perfusion study of

Table 2 Relief of ischaemia in trials comparing a routine invasive with an initial non-invasive strategy in patients with stable coronary artery disease

Study	Routine revascularization, %	Initial medical treatment, %
Kloster *et al.*[74]	ETT 56	58
Dakik *et al.*[88]	SPECT perfusion defect −12	−12
MASS I (CABG)[91]	ETT 28	54
MASS I (PCI)[91]	ETT 34	54
MASS II (CABG)[96,97]	ETT 26	51.1
MASS II (PCI)[96,97]	ETT 36	51
Hambrecht *et al.*[98]	Myocardial perfusion 65 to 78	68 to 77
DECOPI[99]	ETT 22	22
INSPIRE[101]	SPECT perfusion deficit −16	−15
COURAGE[102]	SPECT perfusion deficit −2.7	−0.5
SWISSI II[66]	ETT 12	29

10 627 patients without prior CAD showed an increasing survival benefit of revascularization over medical treatment in patients with moderate to severe ischaemia, whereas no such benefit was apparent in patients with only mild or absence of ischaemia (*Figure 3*).[69] The effect of revascularization on prognosis has also been investigated in a meta-analysis of 24 studies encompassing 3088 patients with left-ventricular dysfunction (mean LVEF = 32 ± 8%) who underwent assessment of viability by means of thallium perfusion imaging, F-18 fluorodeoxy glucose metabolic imaging, or Dobutamine stress echocardiography and were followed for a mean of 25 months.[70] In patients with viability, revascularization was associated with an 80% reduction of risk-adjusted mortality compared with medical treatment (16%/year vs. 3%/year). This benefit was most apparent in patients with impaired left-ventricular function. No benefit was observed in patients without viability at any level of left-ventricular function.

The Alberta Provincial Project for Outcome Assessment in CAD (APPROACH) assessed survival according to treatment allocation in 11 661 patients with multivessel CAD undergoing coronary angiography.[71] Risk-adjusted mortality was significantly lower with both CABG (HR = 0.53, CI 0.46–0.61, $P < 0.001$) and PCI (HR = 0.65, 95% CI 0.56–0.74, $P < 0.001$) compared with medical treatment in the overall cohort as well as patients with three-vessel CAD, whereas CABG was superior to both PCI and medical treatment in the subset of patients with left main CAD.

At Duke University Medical Center, 18 481 patients undergoing coronary angiography between 1986 and 2000 underwent prospective evaluation of risk-adjusted mortality according to treatment assignment.[72] During long-term follow-up revascularization (CABG or PCI) provided a significant survival advantage over medical treatment in patients with low-, intermediate-, and high-severity CAD. The absolute survival advantage amounted to 8, 11, and 24 months of life during 15 years of follow-up comparing CABG with medical treatment. The treatment effect was similar for CABG and PCI in low- and intermediate severity CAD, but CABG prevailed over PCI in high-severity CAD. In the EUROPA study of over 12 000 patients with stable CAD, a risk model was developed. Risk factors for mortality during 4.2 years follow-up included elderly age, a history of MI, stroke or peripheral vascular disease, male gender and diabetes, while previous PCI or CABG was associated with a reduced risk.[26]

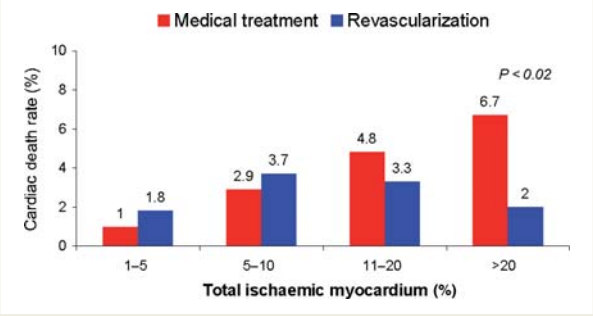

Figure 3 Benefit of revascularization in terms of survival is proportional to the amount of ischaemia as assessed by single photon emission computed tomography imaging prior to revascularization. Obtained with permission from Hachomovits *et al.*[69]

In summary, revascularization is associated with improved clinical outcome in patients with documented moderate-to-severe myocardial ischaemia or viable myocardium, in particular when associated with left-ventricular dysfunction and multivessel CAD.

Randomized trials comparing revascularization with medical treatment

To date 30 randomized trials have compared medical treatment with revascularization by means of PCI or CABG in patients with chronic stable CAD (*Table 3*).[66,67,73–104] The number of patients included into these trials ranged from 44[88] to 2368.[104] Coronary artery bypass surgery was applied as revascularization therapy in 13 trials, of which 6 were performed more than 2 decades ago using predominantly saphenous vein grafts. Balloon angioplasty alone was used in eight studies, whereas subsequent trials reported the use of stents in 9–100% of procedures. Drug-eluting stent implantation was negligible except for BARI-2D (35% of patients). Several trials failed to specify the implemented medical treatment. The majority of studies included predominantly male patients who were relatively young (with the exception of TIME), had preserved left-ventricular function and had not undergone previous revascularization by CABG or PCI. One study enrolled exclusively diabetic patients (BARI-2D).[104] Patients were highly selected as randomization was performed following delineation of coronary anatomy by angiography in the vast majority of studies. By design all trials compared treatment strategies (intention-to-treat, routine revascularization vs. initial medical treatment) allowing subsequent revascularization when patients deteriorated on medical therapy. Such 'cross-over' from medical treatment to revascularization was observed in up to half of patients during follow-up. Accordingly the proportion of patients without revascularization progressively diminished during follow-up, potentially blunting differences between the two strategies.

The largest study comparing PCI with current medical treatment (COURAGE) enrolled 2287 (6.4%) of 35 539 patients undergoing eligibility assessment during a 5 year period.[102] Half of patients had minimal or no symptoms of angina and the extent of ischaemia as assessed by nuclear imaging prior to treatment in a subset of patients was not severe. The rate of death was similar in the PCI (7.6%) and medical therapy group (8.3%, HR = 0.87, 95% CI 0.65–1.16, $P = 0.38$). Non-protocol revascularization procedures were less frequent among PCI patients (21 vs. 33%, HR = 0.60, 95% CI 0.51–0.71) during follow-up.

The recently reported BARI-2D trial randomly assigned 2368 diabetic patients to medical treatment or revascularization, stratified according to choice of PCI (34%) or CABG (16%). Coronary revascularization was performed in 97% of patients in the revascularization and 42% of patients in the medical therapy group during follow-up (*Figure 4*). The use of drug-eluting stents (35%) was low as was the prescription of thienopyridines (21%). At 5 years, mortality did not differ between the medical therapy (13.5%) and the revascularization group (13.2%) in either the CABG or PCI stratum. Major adverse cardiac events (death, MI, or stroke) were fewer among patients allocated to revascularization by

Table 3 Overview of published trials comparing a routine invasive with an initial non-invasive strategy among patients with stable coronary artery disease

	Year	Inclusion criteria	Exclusion criteria	Number of patients: Revasc/OMT	Revasc (PCI, CABG)	PCI Method (PTCA, BMS, DES)	Protocol Revasc. in Revasc.Group	Non-protocol revasc. in Medical Group	CAD severity	Age (years)	Female gender (%)	Diabetes (%)
Mathur and Guinn[73]	1977	Chronic stable CAD	LM-CAD, EF < 15%	56/60	CABG	na	98%	7%	1-vs. CAD 16%; 2-vs. CAD 40%; 3-vs. CAD 53%	54	na	16%
Kloster *et al.*[74]	1979	Chronic stable CAD	ACS within 6 months, CHF	51/49	CABG	na	na	na	1-vs. CAD 18%; 2-vs. CAD 36%; 3-vs. CAD 46%	52	11%	na
ECSS[75]	1979	Chronic stable CAD	na	395/373	CABG	na	93%	13%	2-vs. CAD 40%; 3-vs. CAD 53%; LM-CAD 7%	49	0%	6%
Norris *et al.*[76]	1981	CAD s/P>1 MI	na	50/50	CABG	na	na	18%	2-vs. CAD; 3-vs. CAD	51	na	na
CASS[77]	1984	Chronic stable CAD or s/p MI	LM-CAD, EF < 35%	390/390	CABG	na	92%	24%	1-vs. CAD 27%; 2-vs. CAD 40%; 3-vs. CAD 74%	52	10%	9%
VA Cooperative Study[78]	1984	Stable angina with ischaemia	ACS, CHF	332/354	CABG	na	94%	38%	1-vs. CAD; 2-vs. CAD; 3-vs. CAD	51	0%	15%
ACME-1[79,80]	1992	1-vs. CAD with ischaemia or recent MI	ACS, previous PCI, MVD, EF < 30%	112/115	PCI	PTCA	96%	41%	1-vs. CAD	63	na	18%
TOPS[81]	1992	Recent MI	na	42/45	PCI	PTCA	100%	na	1-vs. CAD	57	16%	21%
Sievers *et al.*[82]	1993	Recent MI, asymptomatic 1-vs. CAD	Previous MI, diabetes mellitus	44/44	PCI	PTCA	100%	20%	1-vs. CAD	56	na	0%
ACME-2[83]	1997	1-vs. CAD with ischaemia or recent MI	ACS, previous PCI, MVD, EF < 30%	51/50	PCI	PCTA	100%	40%	2-vs. CAD	na	na	na
DANAMI[67,84]	1997/2007	CAD with ischaemia or inducible post-infarct ischaemia	Refractory angina, previous revascularization	503/505	CABG (147)/PCI (266)	PTCA	82%	20%	1-vs. CAD; 2-vs. CAD; 3-vs. CAD	56	18%	35%
ACIP[85]	1997	Silent ischaemia	Recent ACS, CCS IV, NYHA III/IV, PCI within 6 mo, CABG within 3 mo, LMD	192/366	CABG/PCI	PTCA	89%	29%	1-vs. CAD; 2-vs. CAD; 3-vs. CAD	61	14%	16%
RITA-2[86,87]	1997/2003	Chronic stable angina	Previous revascularization, recent ACS, LM-CAD	504/514	PCI	BMS 9%	93%	35%	1-vs. CAD 60%; 2-vs. CAD 33%; 3-vs. CAD 7%	58	18%	9%
Dakik *et al.*[88]	1998	CAD with ischaemia s/p MI	EF > 35%, 3-vs. CAD	19/22	PCI	BMS 29%	100%	9%	1-vs. CAD 44%; 2-vs. CAD 41%; 3-vs. CAD 15%	53	41%	na

Continued

Table 3 *Continued*

	Year	Inclusion criteria	Exclusion criteria	Number of patients: Revasc/OMT	Revasc (PCI, CABG)	PCI Method (PTCA, BMS, DES)	Protocol Revasc. in Revasc.Group	Non-protocol revasc. in Medical Group	CAD severity	Age (years)	Female gender (%)	Diabetes (%)
Horie *et al.*[89]	1998	Subacute anterior MI	Age > 80 years, hx of stroke, valvular disease, renal failure, LM-CAD	44/39	PCI	PTCA	na	na	1-vs. CAD 61%; 2-vs. CAD 22%; 3-vs. CAD 17%	62	24%	15%
AVERT[90]	1999	Chronic stable CAD	Age >80 years, recent ACS, 3-vs. CAD, LM-CAD, EF < 40%	177/164	PCI	BMS 30%	94%	12%	1-vs. CAD 56%; 2-vs. CAD 44%	58	16%	27%
MASS I (PCI)[91]	1999	CAD with ischaemia	Prior revasc, MI, LV dysfunction, LM-CAD	72/72	PCI	PTCA	100%	17%	1-vs. CAD	56	42%	18%
MASS I (CABG)[91]	1999	CAD with ischaemia	Prior revasc, MI, LV dysfunction, LM-CAD	70/72	CABG	na	100%	17%	1-vs. CAD	58	42%	19%
TIME[92,105]	2001/2004	CAD with ischaemia, age >75 years	Recent MI	153/148	CABG/PCI	na	71%	42%	1-vs. CAD; 2-vs. CAD; TVD	80	42%	34%
Bech *et al.*[124]	2001	CAD s/p MI	Total occlusion, ACS	90/91	PCI	BMS 46%	100%	7%	1-vs. CAD 67%; 2-vs. CAD 28%; 3-vs. CAD 5%	61	34%	12%
TOAT[94]	2002	CAD s/p anterior MI	na	32/34	PCI	BMS 100%	100%	na	1-vs. CAD	59	20%	14%
ALKK[95]	2003	CAD s/p MI	CCS III/IV, >70% stenosis in Non-IRA, indication for CABG	149/151	PCI	BMS 11%	93%	24%	1-vs. CAD	58	14%	16%
MASS II (PCI)[96,97]	2004/2007	CAD with ischaemia	Previous revasc, ACS, EF < 40%, 1-vs. CAD, LM-CAD	205/203	PCI	BMS 72%	95%	24%	2-vs. CAD 42%; 3-vs. CAD 58%	60	30%	32%
MASS II (CABG)[96,97]	2004/2007	CAD with ischaemia	Previous revasc, ACS, EF < 40%, 1-vs. CAD, LM-CAD	203/203	CABG	na	95%	24%	2-vs. CAD 42%; 3-vs. CAD 58%	60	32%	33%
Hambrecht *et al.*[98]	2004	CAD with ischaemia	ACS, recent MI, EF < 40%, revasc, age >70 years	50/51	PCI	na	100%	6%	1-vs. CAD 30%; 2-vs. CAD 14%; 3-vs. CAD 15%	61	0%	12%
DECOPI[99]	2004	CAD s/p MI without MI	Persistent ischaemia, LM-CAD	109/103	PCI	BMS 80%	5%	1.0%	1-vs. CAD 61%; 2-vs. CAD 26%; 3-vs. CAD 7%	57	10%	16%
OAT[100]	2006	CAD s/p recent MI	Severe CHF, 3-vs. CAD, LM-CAD	1082/1084	PCI	BMS 79%; DES 8%	100%	9%	1-vs. CAD; 2-vs. CAD	59	22%	21%
INSPIRE[101]	2006	CAD with ischaemia and s/p MI	Cardiogenic shock, recurrent chest pain, ACS	104/101	CABG (27)/PCI (43)	BMS 94%	67%	26%	1-vs. CAD; 2-vs. CAD; 3-vs. CAD 33%; LM-CAD 12%	63	24%	28%
COURAGE[102]	2007	CAD	CCS IV, refractory CHF, EF < 30%, LM-CAD	1149/1138	PCI	BMS 91%; DES 3%	96%	33%	1-vs. CAD 31%; 2-vs. CAD 39%; 3-vs. CAD 30%	61	15%	33%

SWISSI II[66]	2007	CAD s/p MI	na	96/105	PCI	na	100%	44%	1-vs. CAD; 2-vs. CAD	55	13%	11%
Nishigaki[103]	2008	CAD with ischaemia	3-vs. CAD, chronic occlusion, ACS, LVEF < 50%, renal failure	192/188	PCI	PTCA 15%; BMS 76%	na	na	1-vs. CAD 68%; 2-vs. CAD 32%	64	25%	40%
BARI 2D[104]	2009	Chronic stable CAD with DM	Urgent revasc, LM-CAD, severe CHF, Creat > 2 mg/dL, hepatic failure	1176/1192	CABG (378)/PCI (798)	na; PTCA 9%; BMS 56%; DES 35%	95%	42% (13% within 6 months)	1-vs. CAD; 2-vs. CAD; 3-vs. CAD 31%	62	30%	100%

Clinical outcome

Study	Year	Follow-up (years)	Primary endpoint		Overall death		Cardiac death		MI	
				Number of patients: Revasc/OMT	Revasc (%)	Medical Rx (%)	Revasc (%)	Medical Rx (%)	Revasc (%)	Medical Rx (%)
Mathur and Guinn[73]	1977	3	na	56/60	5.5	11.7	na	na	10.9	16.7
Kloster *et al.*[74]	1979	3	MACE	51/49	7.8	10.2	na	na	19.6	16.3
ECSS[75]	1979	2	Death and MI	395/373	5.3	7.8	na	na	na	na
Norris *et al.*[76]	1981	4.5	na	50/50	12	10	10	10	na	na
CASS[77]	1984	5	Deasth and MI	390/390	6.7	8.7	na	na	13.6	11.0
VA Cooperative Study[78]	1984	11.2	Death	332/354	42	43	na	na	na	na
ACME-1[79,80]	1997	2.4	Death, MI, rehosp. and revasc.	112/115	13.9	13.4	na	na	12.2	7.1
TOPS[81]	1992	1	LVEF↑ with exercise	42/45	0	0	0	0	9.5	2.2
Sievers *et al.*[82]	1993	2	na	44/44	0	2.3	0	2.3	4.5	0
ACME-2[83]	1997	3	Death, MI, rehosp. and revasc.	51/50	17.6	20	na	na	11.8	12
DANAMI[67,84]	1997/2007	2.4	Death, MI and rehosp. for ACS	503/505	3.6	4.4	na	na	5.6	10.5
ACIP[85]	1997	2	Death, MI, rehosp. and revasc.	192/366	2.2	5.5	na	na	3.6	4.9
RITA-2[86,87]	1997/2003	7	Death and MI	504/514	8.5	8.4	4.0	4.7	6.3	4.5
Dakik *et al.*[88]	1998	1	LV perfusion defect ↓	19/22	4.8	4.3	4.8	4.3	9.5	0
Horie *et al.*[89]	1998	5	Cardiac death, MI and CHF	44/39	2.3	12.8	na	na	6.8	17.9
AVERT[90]	1999	1.5	Cardiac death, cardiac arrest, MI, CVA, rehosp. and revasc.	177/164	0.6	0.6	0.6	0.6	2.8	2.4
MASS I (PCI)[91]	1999	5	Cardiac death, MI and rehosp.	72/72	8.3	8.3	5.6	2.8	5.6	4.2
MASS I (CABG)[91]	1999	5	Cardiac death, MI and rehosp.	70/72	2.9	8.3	2.9	2.8	4.3	4.2
TIME[92,105]	2001/2004	4.1	Death, MI and ACS	153/148	29.4	27.0	20.9	22.3	11.8	12.2
Bech *et al.*[124]	2001	2	Death, MI and revasc.	90/91	2.2	4.4	1.1	2.2	3.3	0
TOAT[94]	2002	1	LV end-systolic volume	32/34	6.3	2.9	na	na	9.4	2.9

Continued

Table 3 *Continued*

	Year	Inclusion criteria	Exclusion criteria	Number of patients: Revasc/OMT	Revasc (PCI, CABG)	PCI Method (PTCA, BMS, DES)	Protocol Revasc. in Revasc.Group	Non-protocol revasc. in Medical Group	CAD severity	Age (years)	Female gender (%)	Diabetes (%)
ALKK[95]	2003	4.7	Death, MI, rehosp. and revasc.	149/151	4.0	11.3	2.7	9.3	6.7	7.9		
MASS II (PCI)[96,97]	2004	5	Death, Q-wave MI and revasc.	205/203	15.5	16.2	11.6	12.3	11.2	15.3		
MASS II (CABG)[96,97]	2004	1	Death, Q-wave MI and revasc.	203/203	12.8	16.2	7.9	12.3	8.3	15.3		
Hambrecht *et al.*[98]	2004	1	Cardiac death, MI, CVA, rehosp. and revasc.	50/51	0	0	0	0	2.0	0		
DECOPI[99]	2004	3	Cardiac death, MI, and ventricular tachyarrhythmia	109/103	7.3	8.7	5.5	6.8	3.7	2.9		
OAT[100]	2006	4	Death, MI, and CHF	1082/1084	9.1	9.4	6.3	5.0	7.0	5.3		
INSPIRE[101]	2006	1	LV perfusion defect ↓	104/101	1.9	1.0	1.9	1.0	4.8	6.9		
COURAGE[102]	2007	4.6	Death and MI	1149/1138	7.4	8.3	2.0	2.2	12.4	11.2		
SWISSI II[66]	2007	10.2	Cardiac death, MI and revasc.	96/105	6.3	21.0	3.1	21.0	11.5	38.1		
Nishigaki[103]	2008	3.25	Death, CVA and rehosp.	192/188	2.9	3.9	na	na	na	na		
BARI 2D[104]	2009	5.3	Death, MI and CVA	1176/1192	11.7	12.2	na	na	na	na		

CAD, coronary artery disease; MI, myocardial infarction; na, not available; CVA, cerebrovascular accident.

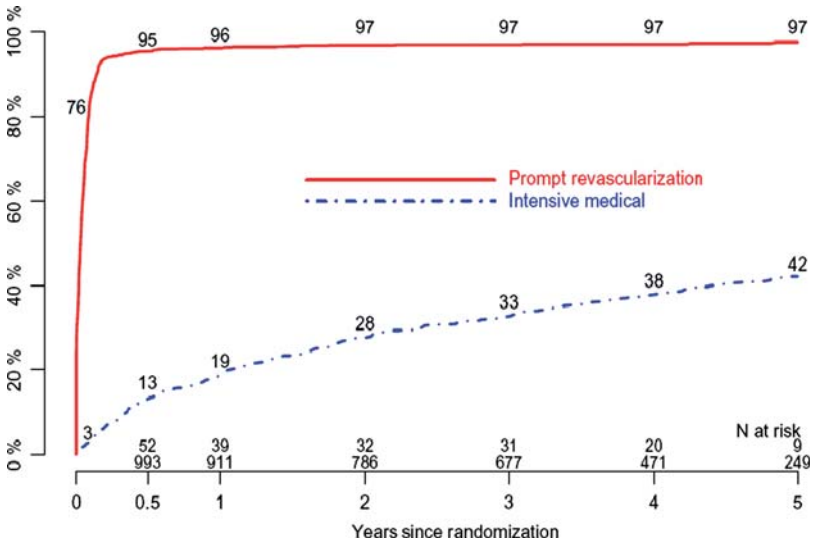

Figure 4 Cumulative rate of revascularization in the BARI-2D trial. ('cross-over') The substantial proportion of patients allocated to medical treatment subsequently undergoing revascularization considerably contributes to the lack of differences in treatment effect between the two strategies. Obtained with permission from Frye *et al.*[104]

CABG (20.9%) than those treated medically (29.9%, $P = 0.01$), whereas no difference was observed in the PCI stratum (23.4 vs. 20.8%, $P = 0.15$).

In contrast, the TIME study, which randomly assigned 301 elderly patients (>75 years of age) to an invasive or medical strategy without baseline coronary angiography, reported no difference in mortality according to initial treatment allocation. Of note, during longer-term follow-up to 4 years survival was significantly lower in patients undergoing revascularization (80%) compared with those not being revascularized (61%, $P = 0.003$) irrespective of the initial treatment assignment.[105]

Since none of these studies was powered to detect a difference in mortality or subsequent MI, meta-analyses are required to assess the impact of revascularization on patient outcome. A meta-analysis of the first seven trials comparing CABG with medical therapy established a reduction in mortality in selected patients following CABG with the benefit being proportional to the number of diseased coronary arteries and the degree of myocardial ischaemia.[106] In contrast, early systematic reviews comparing PCI (mainly balloon angioplasty) with medical treatment in relatively small numbers of patients failed to show a difference in the risk of death or MI.[107–109] More recently, however, a meta-analysis of 17 randomized trials compared medical treatment with PCI in 7513 patients with an average follow-up of 51 months.[110] Revascularization was performed in 92% of patients allocated to PCI (43% balloon angioplasty, 41% stents, 8% CABG), whereas 28% of patients allocated to medical treatment underwent revascularization early or during follow-up. At follow-up, the risk of overall mortality was significantly reduced by 20% in favour of PCI (OR = 0.80, 95% CI 0.64–0.99) with no apparent heterogeneity across trials ($I^2 = 17\%$), whereas the risk of MI was similar among both groups (OR = 0.90, 95% CI 0.66–1.23). Exclusion of four studies allowing both CABG and PCI as treatment option did not impact the results regarding all-cause mortality. The benefit of revascularization became more pronounced with follow-up periods beyond 5 years. A network meta-analysis, however, did not find a significant reduction in mortality or MI for balloon angioplasty (PTCA) compared with medical therapy, nor with bare-metal stents compared with PTCA or drug-eluting stents compared with bare-metal stents. The different results of these meta-analyses reflect differences in the analytic methodology and trial selection, but also illustrate that any mortality benefits of PCI are modest at best.[111]

The most recent review compared medical treatment with surgical or percutaneous revascularization in 13 121 patients enrolled into 17 PCI, 6 CABG, and 5 trials using either revascularization strategy.[112] Consistent with the previous meta-analysis, which covered most of the same trials, mortality was lower after revascularization than in the medical therapy group (7.9 vs. 9.8%, OR = 0.74, 95% CI 0.63–0.88). These findings remained consistent following exclusion of studies in patients with recent MI (OR = 0.77, 95% CI 0.65–0.91). The treatment effect appeared more pronounced in early studies comparing CABG with medical treatment (OR = 0.62, 95% CI 0.50–0.77) than in the more recent studies comparing PCI with medical treatment (OR = 0.82, 95% CI 0.68–0.99). Furthermore, confidence intervals overlapped widely and an analysis of variance revealed no significant difference between the two revascularization strategies ($P = 0.33$)(*Figure 5*). Again, there was no difference in the risk of MI between both groups.

Recently, FFR was compared with angiography for guiding PCI in a large-scale randomized trial with 1005 patients (FAME).[113] At 1 year, routine measurement of FFR to select lesions requiring PCI (FFR < 80%) was associated with lower rates of death or MI (7.3 vs. 11.1%, $P = 0.04$) than PCI guided by angiography alone. Similarly, deferring revascularization in patients with non-significant lesions as determined by FFR appeared safe as shown during the 5 year follow-up

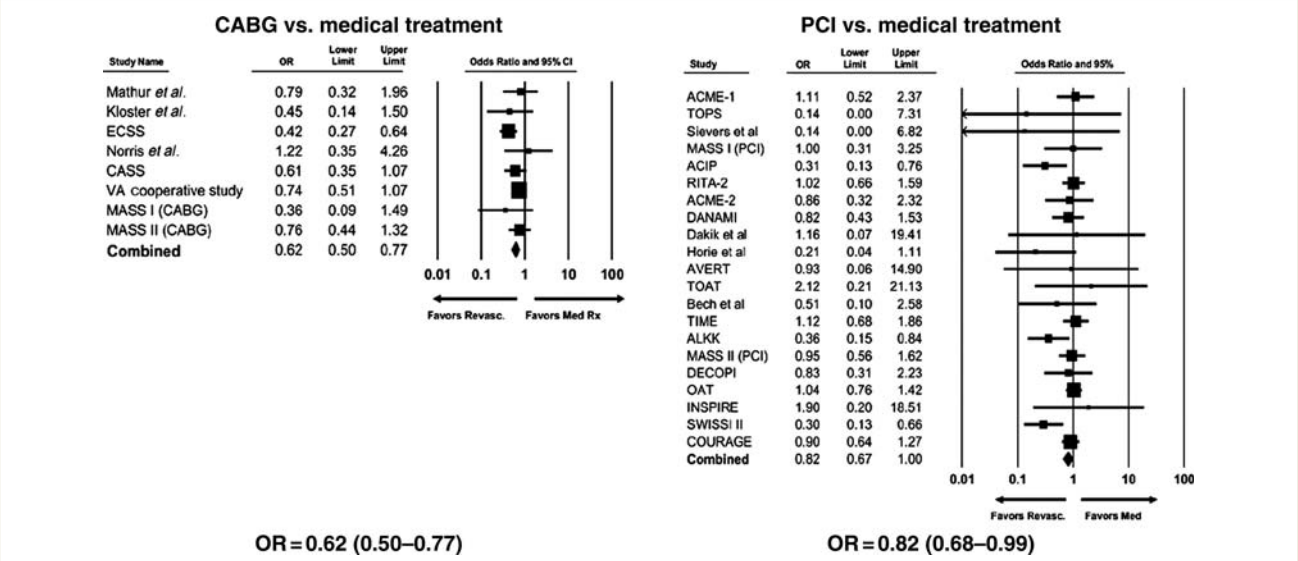

Figure 5 Impact of revascularization on mortality in patients with chronic stable coronary artery disease. Mortality is significantly reduced for the comparison of both coronary artery bypass surgery (OR = 0.62, 95% CI 0.50–0.77) and percutaneous coronary intervention (OR = 0.82, 95% CI 0.68–0.99) compared with medical treatment alone. Obtained with permission from Jeremias *et al.*[112]

of the randomized DEFER study with similar rates of death or MI (<1%/year) among patients treated medically and those undergoing PCI.[40] These findings imply that part of the patients enrolled in previous trials were unlikely to benefit from PCI or CABG if they had no, or limited myocardial ischaemia and suggest that functional assessment of lesions (ischaemia or none) may help to identify those who benefit from revascularization.

Revascularization and quality of life

Compared with medical therapy, revascularization by PCI or CABG has been consistently shown to more effectively relieve angina, reduce the use of anti-angina drugs, improve exercise capacity and quality of life (*Tables 4* and *5*).[107,114] In the RITA-2 and COURAGE studies angina frequency and quality of life were assessed systematically.[115] PCI relieved angina and improved self-assessed health status to a greater degree than medical therapy alone up to 24 months. This benefit from PCI was greatest among patients with severe and frequent angina, and one-third of patients in the medical therapy group subsequently underwent PCI for symptom relief during follow-up. Freedom from angina was 66% in the PCI group of COURAGE when compared with 81% in the PCI group of FAME, a difference which may be explained by the near exclusive use of drug-eluting stents, reducing the rate of restenosis, in the latter.[113] Indeed, a recent meta-analysis showed sequential reductions in repeat revascularization with bare-metal stents compared with balloon angioplasty (risk reduction 32%) and with drug-eluting stents compared with bare-metal stents (risk reduction 56%), which undoubtedly impact quality of life.[111]

The debate

The presentation and publication of the COURAGE study caused a heated debate, particularly among colleagues from the USA.[17,116]

Table 4 Freedom from angina in trials comparing a routine invasive with an initial non-invasive strategy in patients with stable coronary artery disease

Study	Routine revascularization, %	Initial medical treatment, %
Mathur and Guinn[73]	62	7
Kloster *et al.*[74]	69	47
ACME-1[79,80]	63	48
Sievers *et al.*[82]	80	75
ACME-2[83]	53	36
RITA-2[86,87]	63	46
MASS I (CABG)[91]	73	26
MASS I (PCI)[91]	65	26
Bech *et al.*[124]	51	70
ALKK[95]	77	61
MASS II (CABG)[96,97]	74	55
MASS II (PCI)[96,97]	77	55
DECOPI[99]	93	89
OAT[100]	89	91
COURAGE[102]	74	72

The validity of COURAGE was called into question owing to the inclusion of only 6.4% of the screened population, the relatively high proportion of patients lost to follow-up, the inclusion of patients with little or no ischaemia, allocation of treatment only after coronary angiography excluding patients at increased risk, and question marks regarding the quality of revascularization procedures in various health care settings. Moreover, the study was judged to be underpowered due to lower than expected event rates despite protocol amendments allowing for more liberal

Table 5 Proportion of patients requiring anti-angina drugs in trials comparing a routine invasive with an initial non-invasive strategy in patients with stable coronary artery disease

Study	Routine revascularization, %	Initial medical treatment, %
Kloster *et al.*[74]	57	51
ACME-1[79,80]	53	97
ACME-2[83]	62	96
RITA-2[86,87]	64	86
AVERT[90]	50	60
Bech *et al.*[124]	45	39
ALKK[95]	36	55
INSPIRE[101]	≥2 in 36	≥2 in 70
COURAGE[102]	40	57
SWISSI II[66]	12	47
Nishigaki[103]	36	54

inclusion and extension of follow-up. The definition of peri-procedural infarction with any increase of CK-MB was felt oversensitive without clear prognostic relevance and not adhering to recommendations of published guidelines thus disadvantaging the PCI group.[41] Finally, cross-over from medical treatment to subsequent revascularization was not considered an adverse event but said to camouflage potential differences in outcome between the two treatment regimens. Notwithstanding these limitations, COURAGE and other individual studies have failed to show any superiority of PCI in terms of ischaemic endpoints (*Table 3*). Earlier trials comparing an initially invasive- or non-invasive strategy in stable CAD were relatively small and under powered, particularly when compared with studies which assess preventive treatment with drugs including several thousand of patients.[24,55,56,117,118] Yet the results of meta-analyses of revascularization trials have shown a consistent benefit in terms of survival for CABG and a modest survival benefit for PCI.[106,110,112] Moreover, the data from large observational studies support the notion of a graded survival benefit derived from both revascularization procedures.[71,72]

The debate elicited by COURAGE has called our attention to the fact that, apart from many patients who appropriately benefit from PCI and CABG, the indications for such procedures in other patients are less well defined. Revascularization is primarily directed against the elimination of myocardial ischaemia as well as symptoms of affected patients. Thus, treatment of coronary lesions without ischaemia or of patients without symptoms is not beneficial. Yet, about half of the patients undergoing elective PCI for stable angina in the UK[119] and in the USA[14] do not undergo a stress test to document ischaemia before the procedure. Worldwide, inappropriate revascularization procedures increase healthcare cost and use scarce hospital resources.

Conclusions

All patients with atherosclerosis, including patients with angina pectoris, benefit from life long drug therapy in addition to a healthy lifestyle. In addition coronary revascularization is appropriate at some time or several times during their lifespan, either for episodes of ACSs or for treatment of myocardial ischaemia. Optimal management of CAD, as presented in ESC guidelines[18,52] and similar publications includes: (i) appropriate lifestyle, i.e. no smoking, a healthy diet, weight control, and regular exercise; (ii) detection and treatment of diseases and conditions which increase the risk of atherosclerosis, in particular hypertension, diabetes, and hypercholesterolaemia; (iii) drug therapy to lower LDL cholesterol (statins) in subjects at high risk for new or recurrent atherosclerosis events; (iv) additional preventive therapy with aspirin, other anti-thrombotic agents, ACE-inhibitors, and β blockers in patients with known atherosclerosis; (v) symptomatic treatment with nitrates, β blockers, calcium channel blockers, and other anti-angina drugs; and (vi) revascularization by PCI or CABG in selected patients.

Revascularization exerts favourable effects on symptoms, quality of life, exercise capacity, and survival, particularly in those with extensive CAD and documented moderate-to-severe ischaemia. Accordingly, CABG and PCI should be considered a valuable adjunct rather than an alternative to medical therapy. Of note, the benefits of revascularization are associated with a low peri-procedural risk and therefore justify their implementation for symptomatic as well as prognostic reasons. As with most other therapeutic interventions in medicine, the relief of symptoms remains a noble task of physicians caring for patients with stable CAD, particularly in today's executive society where only few would opt to accept angina symptoms impeding their otherwise active life style.

The debate should not be medical vs. revascularization therapy but rather which patients should be offered revascularization and when. The timing of revascularization requires careful consideration. Patients with no or mild symptoms and little ischaemia can safely be treated with medical treatment alone. Conversely, patients with moderate-to-severe symptoms and/or extensive ischaemia should be strongly considered for revascularization therapy. Non-invasive (MS-CT, perfusion scintigraphy, or PET-CT) or invasive (FFR) identification of lesions giving rise to ischaemia may further improve outcome in patients submitted to revascularization. Patients undergoing coronary angiography for symptomatic CAD with an anatomy amenable to PCI should be offered the possibility to undergo revascularization during the same session (ad hoc) as treatment options (medical treatment, CABG, and PCI) are known and can be discussed in advance, sparing yet another invasive procedure. Finally, patient preference must be carefully weighed in the overall treatment selection.

We call upon our colleagues to review their practice and to comply with the recommendations for optimal medical management of all patients with angina and stable CAD as well as optimal use of PCI and CABG in appropriately selected patients.

Conflict of interest: none declared.

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